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REVIEW

Nystagmus

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Purpose of review
The clinical and laboratory assessment of nystagmus in patients with neurologic disorders can provide crucial elements for a state-of-the-art differential diagnosis. An increasing number of publications in the fields of neuro-otology and neuro-ophthalmology have nystagmus in the center of interest, which makes frequent updates on the diagnostic and therapeutic relevance of these contributions indispensable. This review covers important clinical studies and studies in basic research relevant for the neurologist published from January 2016 to August 2017.

Recent findings
Current themes include vestibular nystagmus, positional nystagmus, optokinetic nystagmus and after-nystagmus, vibration-induced nystagmus, head-shaking nystagmus, postrotatory nystagmus, caloric nystagmus, nystagmus in cerebellar disorders, differential diagnosis of nystagmus and treatment approaches (whereas infantile nystagmus syndrome is not addressed in this review). These studies address mechanisms/pathomechanisms, differential diagnoses and treatment of different forms of nystagmus.

Summary
In clinical practice, a structured description of nystagmus including its three-dimensional beating direction, trigger factors and duration is of major importance. The differential diagnosis of downbeat nystagmus is broad and includes acute intoxications, neurodegenerative disorders and cerebrovascular causes amongst others. In patients with positional nystagmus, the distinction between frequent benign peripheral and rare but dangerous central causes is imperative.

Keywords
cerebellum, downbeat nystagmus, eye movements, positional nystagmus, vestibulo-ocular reflex

INTRODUCTION

Nystagmus refers to repetitive, to-and-fro movements of the eyes that are initiated by slow phases [1]. Different types of nystagmus can be distinguished based on the presence of fast and slow phases (jerk nystagmus) or alternating slow phases (pendular nystagmus). In the assessment of nystagmus, a structured approach is essential, as the differential diagnosis of nystagmus is very broad. This includes both benign peripheral-vestibular disorders and dangerous potentially life-threatening central causes. In this review, we summarize recent advances in the assessment of nystagmus in both healthy human individuals and patients. Separate sections will address different forms of nystagmus, including vertical nystagmus, positional nystagmus, head-shaking and vibration-induced nystagmus and vestibular nystagmus. Note that this review does not address publications on infantile nystagmus syndrome (congenital nystagmus).

VESTIBULAR NYSTAGMUS

Of major importance is the distinction between peripheral-vestibular and central nystagmus. The presence of anticompensatory eye movements (AQEM) during video head impulse testing was proposed to be predictive for a peripheral-vestibular origin of spontaneous nystagmus compared with central causes [2]. Recently, nystagmus was assessed during Menière attacks. Although the beating direction was towards the affected side in two patients with unilateral Menière's disease, suggesting an irritative nystagmus in the acute phase [3], ictal

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KEY POINTS

- A structured description of nystagmus including its three-dimensional beating direction, trigger factors and duration is recommended.
- In patients with positional nystagmus, the distinction between frequent benign peripheral and rare but dangerous central causes is imperative.
- The differential diagnosis of downbeat nystagmus is broad and includes acute intoxications, neurodegenerative disorders and cerebrovascular causes amongst others.

downbeat nystagmus (DBN) was reported in a patient with bilateral Menière's disease, possibly because of posterior canal inhibition [4]. Whereas pure vertical nystagmus is typically of central origin, bilateral superior canal plugging in two patients with bilateral superior canal dehiscence resulted in vibration-induced upbeat nystagmus, reflecting an unusual peripheral cause for upbeat nystagmus [5].

POSITIONAL NYSTAGMUS

Positional vertigo and nystagmus may present a diagnostic challenge. Although most frequently observed in benign paroxysmal positional vertigo (BPPV), central disorders may result in positional nystagmus as well. Rates of asymptomatic positional nystagmus in healthy controls reach almost 90% [6]. A recent systematic review on clinical and radiological findings in lesion-induced central positional nystagmus concluded that better phenotyping of central positional nystagmus is needed to allow a reliable discrimination from peripheral causes [7▪].

The bow and lean test can be useful in identifying the type (geotropic versus apogeotropic variant) and side (right versus left) of lateral canal BPPV. In a recent study, evaluating nystagmus intensity and direction with the head bent forward ('bow') and backward ('lean'), correct identification was achieved in 79% of patients [8▪]. Noteworthy, positional nystagmus may show a change in beating direction over time. Short-term adaptation of the vestibulo-ocular reflex has been proposed to explain the formation of direction-reversing nystagmus, which was found more frequently in lateral canal BPPV compared with posterior canal BPPV [9]. Paroxysmal positional nystagmus may also be associated with a fistula between the lateral canal deformity and an enlarged vestibular aqueduct [10].

In supine position, lateral canal BPPV may mimic spontaneous nystagmus. Such ''pseudo-spontaneous' nystagmus was more frequent in patients with lateral canal cupulolithiasis than canalolithiasis (93 vs. 41%) and is likely mediated by the natural inclination of the lateral canal and the medial-to-lateral orientation of the cupular axis in cupulolithiasis and by direction-reversing nystagmus in canalolithiasis [11].

Persistent geotropic direction-changing positional nystagmus (DCPN) with neutral position and cupulolithias of the lateral canal was recently characterized by a short clinical course and frequent recurrence [12]. Noteworthy, those patients with long-duration geotropic DCPN did not benefit from canalith-repositioning procedures, suggesting that the underlying disorder is not linked to free-floating debris but rather to deflection of the cupula [13].

New insights into mechanisms of the light cupula syndrome were described in two case reports: whereas heavy endolymph was proposed as a mechanism for persistent positional vertigo and geotropic positional nystagmus in a patient with meningitis and high cerebrospinal fluid (CSF) protein [14], a light cupula of a posterior canal was suggested in a case with persistent torsional DBN [15]. Novel therapeutic strategies in geotropic DCPN include treatment with transcutaneous vagus nerve stimulation [16], that led the authors to propose a top-down mechanism that normalized lateral canal hyperexcitability. In patients with vestibular migraine and positional vertigo, prophylactic treatment with cinnarizine or topiramate resulted in cessation of symptoms in 92% of patients [17].

OPTOKINETIC NYSTAGMUS AND AFTER-NYSTAGMUS

Optokinetic nystagmus (OKN) is elicited by full-field visual movement, whereby both the smooth pursuit system (via the foveal retina) and the optokinetic system (via the extra-foveal retina) are stimulated. The contribution of the optokinetic system to the overall ocular motor response during full-field visual movement is reflected in the optokinetic after-nystagmus (OKAN), which can be observed whenever OKN is terminated by a sudden switch to total darkness. The gain of the optokinetic nystagmus is defined by dividing the velocity of the nystagmus slow phase by the velocity of the visual stimulus. The generation of OKN fast phases is a biological time process that can be influenced by a concurrent cognitive task [18▪]. Measuring the optokinetic response may be used as an objective measure of contrast sensitivity function [19] or visual acuity [20].

OKN can be suppressed by looking at a space-fixed fixation light. If, during that task, patients have to detect the appearance of additional targets

without looking at them, the OKN is less suppressed and the effect of this divided attention is more pronounced if the additional target is moving [21]. Whenever oppositely directed optokinetic stimuli are presented simultaneously in different areas of the visual field, attention to one of the fields increases the gain of the OKN in the direction of the visual stimulus in this field [22].

The time constant of the OKAN reflects the effectiveness of the velocity-storage mechanism, which, in turn, plays an important role in motion sickness [23]. Accordingly, a strong positive correlation between the OKAN time constant and the susceptibility to visually induced motion sickness was found [24].

Whenever a horizontal optokinetic stimulus is projected for 2 s on the two eyes, but with an opposite movement direction, the OKN and the perceived movement point in the same direction in both healthy individuals and patients with Parkinson's disease; thus, OKN in this paradigm can be used to indicate conscious motion perception [25].

VIBRATION-INDUCED NYSTAGMUS

Vibration-induced nystagmus is elicited by pressing a vibrating device perpendicularly to the skin over the mastoid process, typically during 20 s. In patients with a unilateral vestibular hypofunction, this bone-conducted vibration induces predominantly horizontal nystagmus in the direction of the unaffected ear. In some patients with Menière's disease or vestibular schwannoma, however, vibration-induced nystagmus may also be directed towards the affected ear [26].

Vibration-induced nystagmus is time-locked with the stimulus, should be observed under Frenzel or infrared-video goggles, and is most robust at a stimulus frequency of 100 Hz [27]. Previously, the most common used frequencies were between 30 and 60 Hz [28]. On the basis of measurements with piezo-electric and force sensors, vibration is more effective on the mastoid than on the posterior cervical muscles and more effective if the apparatus is held by the dominant hand of the examiner [29]. In patients with vestibular schwannoma, nystagmus induced by vibration of the ipsilateral sterno-cleido-mastoid muscle correlated with tumor size [30].

HEAD-SHAKING NYSTAGMUS

Head-shaking nystagmus, or, more precisely, nystagmus after horizontal head shaking, can be observed in patients with peripheral or central asymmetries of vestibular signals between the two sides. Typically, head-shaking nystagmus is horizontal. In some patients with central lesion, head-shaking nystagmus may be vertical. This nystagmus is called perverted head-shaking nystagmus. Patients with perverted head-shaking nystagmus frequently show impaired tilt suppression of postrotatory nystagmus [31]. Also, there is an association between perverted head-shaking nystagmus and essential tremor [32].

Perverted head-shaking nystagmus is usually downbeat, rarely upbeat, and a correlation with specific MR-lesions was not found so far [33]. Considering the three-dimensional angular velocity axis and the slow-phase velocity time constant, perverted downbeat head-shaking nystagmus is probably the result of increased activity of the central anterior canal pathways [34▪].

POSTROTATORY NYSTAGMUS

Postrotatory nystagmus is a vestibular nystagmus elicited by rapid deceleration of a turntable from constant-velocity to zero-velocity rotation about an earth-vertical axis. Typically, patients are in an upright position, and the axis of deceleration passes through the center of the inter-aural line. The slow-phase velocity of horizontal postrotatory nystagmus in the dark decays with a time constant (usually between 5 and 10 s) determined by the velocity-storage mechanisms of the brainstem and cerebellum. Tilting the head or whole body immediately or a few moments after the end of deceleration suppresses postrotatory nystagmus and therefore, decreases the time constant of the slow-phase velocity decay. In addition, the angular slow-phase velocity axis of the eyes shifts in the direction of the gravity vector. In some patients, this tilt suppression of postrotatory nystagmus causes vertigo, disorientation or motion sickness because of the conflict of signals from the semicircular canals and the otoliths. Patients with impaired tilt suppression of postrotatory nystagmus frequently show perverted head-shaking nystagmus [31].

Tilt suppression of postrotatory nystagmus of patients with vestibular migraine differs from healthy individuals and patients with migraine headaches: the angular slow-phase velocity axis of the eyes shows a larger shift in the direction of the gravity vector, but this effect is not correlated with the shortening of the slow-phase velocity time constant [35]. Whether the resulting 'residual sensory conflict' explains the motion sickness susceptibility of the patients with vestibular migraine needs to be further explored [36].

Whenever postrotatory nystagmus is not modified by a tilt, but by centrifugation without an

angular movement (so-called double centrifugation), the time constant of the slow-phase velocity decay is not affected [37]. Thus, otolith signals alone – in this case oscillating inter-aural and naso-occipital translatory signals – do not interfere with the velocity-storage mechanism.

To simulate the effect of horizontal spontaneous nystagmus on the high-acceleration vestibulo-ocular reflex, healthy individuals were assessed with the video head impulse test. It was found that the slow-phase velocity of postrotatory nystagmus and the velocity of the head-impulse evoked eye movements simply added; thus, to compute the correct gain of the vestibulo-ocular reflex during head impulses, one should subtract the velocity of the baseline eye drift [38].

CALORIC NYSTAGMUS

Irrigation of the external auditory canal with warm or cold water elicits a mainly horizontal nystagmus, so-called caloric nystagmus. As the cold or warm temperature from the external auditory canal reaches the lateral semicircular canal through the mastoid bone, the individual anatomy of this bone could determine the intensity of the evoked caloric nystagmus. In a preliminary study, is was found that the amount of airspace in the mastoid bone is inversely related to the effectiveness of warm caloric irrigation [39▪]. Mental tasking, on the other side, does not influence the parameters of caloric nystagmus [40].

Strong cold-water irrigation with 24 °C reduces the gain of the vestibulo-ocular reflex during ipsilateral head impulses, whereas weaker cold-water or warm-water irrigation has no effect on the result of the head impulse test [41]. The strong cold-water irrigation may shift the set point of the nonlinear relation between head acceleration and the vestibular firing rate toward a less acceleration-sensitive zone, thus, demonstrating Ewald's second law in healthy individuals.

NYSTAGMUS IN CEREBELLAR DISORDERS

To better understand the impact of vertical nystagmus in patients, knowing its prevalence in the general population is important. A recently developed nystagmus-specific quality-of-life questionnaire can help to determine the impact of nystagmus on daily living [42]. In a recent study, spontaneous upbeat nystagmus in supine position was noted in almost half of all healthy participants and was linked to individual structural differences in cerebellar tonsil volume [43▪]. Positional DBN and perverted head-shaking nystagmus seem to be associated with essential tremor, as these findings were more prevalent than in controls (21.2 vs. 3.9%) [32]. Acute-onset nystagmus may be seen in cases with drug intoxication (as, e.g. acute DBN in oxcarbazepine intoxication, see Fig. 1 [44]) or pesticides (avermectins [45]). However, also therapeutic doses of commonly prescribed drugs may trigger DBN and dizziness, as reported for pregabalin [46] and lithium [47], being reversible after cessation in both cases. Blocking of the excitatory responses of vestibular nuclei neurons may explain DBN because of a

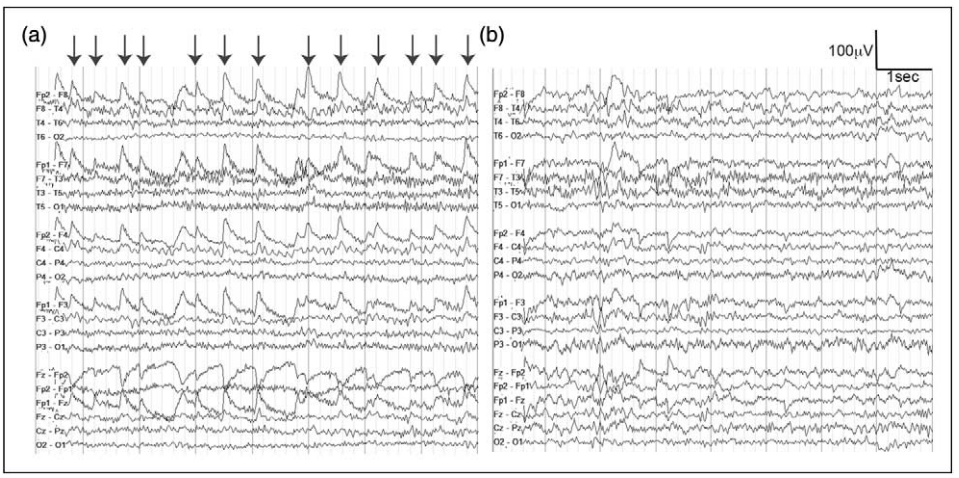

FIGURE 1. Electroencephalography (EEG) recording in longitudinal bipolar montage (10/20 system). Panel A: at the time of oxcarbazepine intoxication (day 3), steep surface-negative excursions (arrows) are followed by more slow return to baseline. Considering eyeball polarity (positive to negative from ventral to caudal), this indicates slow upward eye-drift followed by fast downward saccades, consistent with DBN. Note that eyelid movements will contribute to these EEG changes as well. Panel B: 48 h later DBN had resolved, consistent with the return of oxcarbazepine blood levels to the therapeutic range. This figure was originally published in Ref. [44].

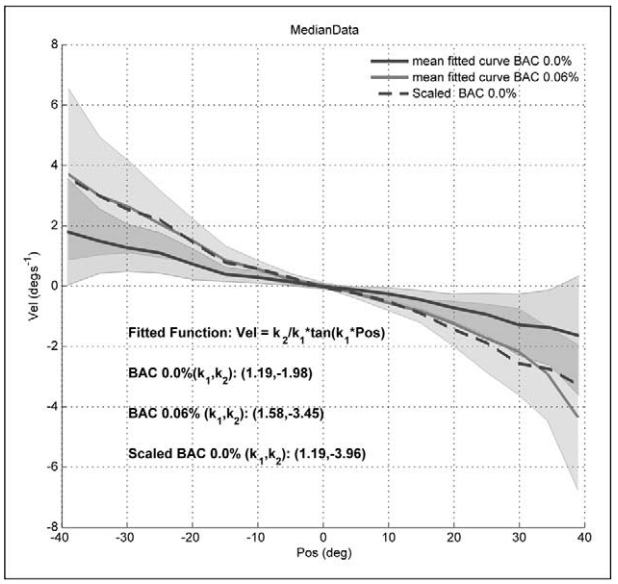

FIGURE 2. Blood alcohol content (BAC) on eye-drift velocity as a function of eye gaze angle. Effect of 0.6‰ BAC on eye-drift velocity as a function of eye gaze angle. Each line represents the mean drift velocity of all individuals in the different conditions, whereas the shaded area represents the mean (SD). The light grey dashed line is a scaled version of the data recorded before alcohol intake (dark grey dashed line), perfectly overlapping with the data recorded after alcohol intake (black solid line), confirming the pure scaling effect of 0.6‰ BAC. Such an effect is further confirmed by the scaling parameter of the tangent model (k2), which was estimated on the plotted curves (the estimated parameters are reported in the figure). This figure was originally published in Ref. [49▪].

selective histamine H2 receptor antagonist (ranitidine) [48].

As a novel human model to study effects of cerebellar loss-of-function on gaze-holding properties, controlled alcohol intake was proposed [49▪]. At a blood-alcohol content of 0.06%, horizontal eye-drift velocity approximately doubled at all eccentricities studied (Fig. 2), matching the pattern of gaze-holding deficits previously noted in late-onset neurodegenerative cerebellar disease.

During the diagnostic procedure for new-onset nystagmus, caution is advised for patients with apogeotropic positional nystagmus during supine-roll testing whenever repeated repositioning maneuvers remain without success. In these patients, midline cerebellar mass lesions may mimic BPPV [50].

NYSTAGMUS IN THE DIFFERENTIAL DIAGNOSIS

The localizing value of ocular motor findings was emphasized in a patient with conjugate ipsilesional eye deviation and spontaneous horizontal nystagmus beating contralesionally in lateral medullary infarction [51]. Sub-acute onset of upbeat nystagmus and gaze-evoked nystagmus in combination with neurocognitive deficits and neuropathy after bariatric surgery should raise a high suspicion of Wernicke encephalopathy and prompt immediate treatment with parenteral thiamine [52].

Acquired periodic alternating nystagmus (PAN) was linked to autoimmune disorders and long-term lithium intake, promoting the application of intravenous immunoglobulin in the first case [53] and prescription of baclofen in the latter case [54]. In a patient with systemic lupus erythematous and cerebellar atrophy, amantadine reduced PAN, dizziness and oscillopsia [55]. Lacking central (cerebellar) adaptive recalibration because of profound visual loss has been proposed to explain windmill nystagmus, a rare type of nystagmus that is characterized by a clock-like rotation of the nystagmus beating direction [56].

Ocular motor cerebellar signs and ataxia of gait/stance may precede classical features in sporadic Creutzfeldt–Jakob disease [57] and may reflect prominent features in immune-mediated anti-DPPX encephalitis [58]. Hereditary cerebellar neurodegeneration may initially present as (positional) DBN, as described for spinocerebellar ataxia type 6 [59] and X-linked adrenoleukodystrophy [60]. Hypometric horizontal saccades, disconjugate gaze-evoked nystagmus and esotropia may represent prominent features in central nervous system Whipple's disease [61].

In children, vertical nystagmus may be linked to retinal dystrophies [62]. Different nystagmus patterns may be seen in newborn and infants with Joubert syndrome [63], mutations in the calcium/calmodulin-dependent serine protein kinase (*CASK*) gene leading to FG-syndrome 4 [64], visual deprivation from child neglect [65], mass lesions above the midbrain [66] and galactokinase deficiency [67]. The differential diagnosis of isolated nystagmus in pediatric patients remains challenging. In a case series of 148 children with isolated nystagmus, only 23 (15.5%) had abnormalities on brain MRI, with abnormal signal lesions, Chiari type 1 malformations and optic glioma most frequently reported [68].

TREATMENT APPROACHES TO NYSTAGMUS AND OSCILLOPSIA

A broad range of drugs has been investigated regarding their effect on different forms of nystagmus [69▪]. For channelopathies as familial hemiplegic migraine, acetazolamide is effective for treating

disequilibrium and positioning DBN [70]. In autoimmune-mediated glutamic acid decarboxylase (GAD)-associated cerebellar ataxia, intravenous immunoglobulin successfully treated paroxysmal positioning upbeat nystagmus [71].

Novel noninvasive therapeutic approaches to reduce DBN include real-time computer-based visual feedback, reducing slow-phase vertical eye movements and improving visual acuity in 5 of 10 patients [72▪] and resting in darkness for 2 h (compared with remaining in bright light), resulting in a relative reduction of vertical slow-phase eye velocity by about one-third [73]. Advanced therapeutic interventions in acquired nystagmus include the attachment of a T-plate to the lateral orbital rim and the inferior rectus muscle tendon [74], the implantation of an oculomotor prosthesis [75] and retrobulbar botulinum-toxin A injections [76], resulting in reduced nystagmus amplitude and oscillopsia in all cases. Lateral canal occlusion was confirmed as a valuable treatment option for head-shaking nystagmus and vertigo in a patient with head-jolting nystagmus syndrome [77].

CONCLUSION

Nystagmus is a frequent sign in patients with neurological disorders. Physiological nystagmus includes rotatory and postrotatory nystagmus, OKN and after-nystagmus, as well as symmetric caloric nystagmus. Pathological nystagmus includes spontaneous nystagmus, positional nystagmus, vibration-induced nystagmus, head-shaking nystagmus and asymmetric caloric nystagmus. The differential diagnosis and therapy of pathological nystagmus relies on an increasing body of information detailing the mechanisms or pathomechanisms of different forms of nystagmus.

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Conflicts of interest

There are no conflicts of interest.

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